Journal of Surgical Oncology 1999;70:95–99

Primary Tumors of the Mediastinum

BRIAN P. WHOOLEY, MD, JOHN D. URSCHEL, MD,* JOSEPH G. ANTKOWIAK, MD, AND HIROSHI TAKITA, MD

Department of Thoracic Surgical Oncology, Roswell Park Cancer Institute, Buffalo, New York

Background and Objectives: Diagnostic and therapeutic approaches to mediastinal tumors have changed over the past three decades. We reviewed our recent experience with these tumors and assessed the role of a multidisciplinary treatment approach.

Methods: A retrospective review of 124 patients with primary mediastinal tumors over a 25-year period.

Results: Median age was 35 years. Symptoms were present in 86 of 124 (69%) patients. One hundred and eleven of 124 (90%) tumors were malignant. Distant metastases were present at diagnosis in 14 of 124 (11%) patients. The most common tumor was thymoma (38/124, 31%), followed by germ-cell tumor (29/124, 23%), lymphoma (24/124, 19%), and neurogenic tumors (15/124, 12%). Seventy-four of 124 (60%) patients underwent resection, 88 (71%) received chemotherapy, and 97 (78%) received radiation therapy. Tumor recurrence occurred in 52% (47/91) of patients who initially had a complete resection or response to treatment. Median time to recurrence was 10 months. Overall median survival was 44 months. Metastatic disease at presentation ($P = 0.02$) and tumor recurrence ($P = 0.00001$) were the only significant independent predictors of survival on multivariate analysis.

Conclusions: Malignant primary mediastinal tumors often require multimodality treatment. Despite improvements in survival with multimodality treatment, death from recurrent disease remains a problem.

J. Surg. Oncol. 1999;70:95–99. © 1999 Wiley-Liss, Inc.

KEY WORDS: **mediastinal neoplasms; neoplasms; germ cell; thymoma; lymphoma; chemotherapy**

INTRODUCTION

Mediastinal neoplasms are uncommon tumors. They often present a diagnostic and therapeutic challenge for surgical oncologists. Much of our knowledge about these tumors is derived from single institution series, which often span as many as 50 years and often include a majority of benign lesions [1,2]. Significant advances in the evaluation and diagnosis of these lesions have occurred in the last 2 decades with the introduction of computerized tomography (CT), interventional radiology biopsies, tumor markers, and immunohistochemical techniques. Multimodality treatment has contributed to improved survival for many malignant mediastinal tumor histologies.

The purpose of this study was to evaluate a modern series of patients with mediastinal tumors who were treated at a tertiary referral cancer hospital. The aim was to review our data on presentation, diagnosis, management, and outcome of patients with mediastinal tumors, with a particular emphasis on malignant lesions treated in a multidisciplinary setting.

MATERIALS AND METHODS

We performed a retrospective review of all patients with mediastinal tumors treated at Roswell Park Cancer Institute between 1 January 1971, and 31 December

*Correspondence to: John D. Urschel, MD, Department of Thoracic Surgical Oncology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. Fax No.: (716)282-4186.

Accepted 24 November 1998

© 1999 Wiley-Liss, Inc.

TABLE I. Presentation of Mediastinal Tumors

Symptoms (n = 124)		Physical examination	
Pain	37	Normal	78
Cough	28	Respiratory signs	12
Dyspnea	23	SVC[a] syndrome	13
Swelling	11	Myasthenia gravis	4
Fever	13	Horner's syndrome	2
Fatigue	10	Chest wall/neck mass	4
Weight loss	8	Other	11
Hemoptysis	5		
Hoarseness	2		

[a]SVC, superior vena cava.

1996. Records were reviewed for patient demographics, clinical presentation, diagnostic methods, tumor characteristics, patient management, and outcome. Tumor location was designated as anterosuperior, middle, or posterior mediastinal [3]. Pediatric patients were defined as those less than 18 years of age. Only lymphomas that were confined solely to the mediastinum were included. Follow-up was available on 94% of the cases. Survival was calculated from the date of diagnosis to the date of last follow-up or death. Survival rates were estimated by the Kaplan-Meier method [4], and log rank analysis was used to compare survival distributions among subgroups. Multivariate analysis was carried out with the Cox's proportional hazards model using the step-down method. Mean values were compared using a two-tailed *t*-test. Statistical analysis was done using SPSS for Windows software (SPSS, Chicago, IL).

RESULTS

One hundred and twenty-four patients with primary mediastinal tumors were treated at Roswell Park Cancer Institute over the 25-year study period. Seventy-six were male and 48 were female. The mean age was 35 years, ranging from newborn to 84 years. Patients with thymoma were significantly older (mean age, 48 years; $P = 0.0001$) and patients with neurogenic tumors were significantly younger (mean age, 19 years; $P = 0.001$) than patients with other tumor types. There were 20 pediatric patients.

Malignant tumors were symptomatic in 75% (83/111) of cases, while benign tumors were asymptomatic in 77% (10/13) of patients. The most common symptoms were pain, cough, and dyspnea (Table I). Approximately two-thirds of patients had no significant abnormality on physical examination. Superior vena cava syndrome was present in 13 patients, while 4 patients presented with myasthenia gravis. Almost all patients (116/124, 94%) had an abnormality visible on standard chest radiography. In addition, patients in the latter half of the study period were routinely examined by chest computed tomography (CT). Magnetic resonance imaging (MRI) was used selectively (seven patients) to assess for possible spinal and vascular invasion.

One hundred and two of 124 (82%) tumors were located in the anterosuperior mediastinum. However, in the pediatric population, the tumors were evenly distributed between the anterosuperior and posterior mediastinum (Fig. 1). Tumors were malignant in 111 of 124 cases (90%) and benign in 13. The most common tumor histology was thymoma (38/124 patients, 31%), followed by germ-cell tumor (29/124, 23%), lymphoma (24/124, 19%), and neurogenic tumors (15/124, 12%) (Table II). There were 38 thymomas, of which 29 were invasive. Nonseminoma accounted for 15 of 29 germ-cell tumors, while 8 were seminoma, 3 indeterminate, and 3 benign teratomas. There were 24 lymphomas, of which 18 were non-Hodgkin's and 6 were Hodgkin's type. Neurogenic tumors accounted for 50% (10/20) of the pediatric tumors. All neurogenic tumors occurred in the posterior mediastinum and neuroblastoma was the most common histology (six patients). There were three carcinoid tumors (all thymic) and five benign cysts (three thymic, one pericardial, one bronchogenic). At the time of initial diagnosis, regional nodal metastasis were documented in 44 patients and distant metastases were present in 14.

Complete surgical resection was carried out in 53 patients, subtotal resection was done in 21, and 50 tumors were not resected. Resection was performed in 66% (25/38) of thymomas, 69% (20/29) of germ-cell tumors, 73% (11/15) of neurogenic tumors, and 25% (6/24) of lymphomas. Median sternotomy was the most common surgical approach (45 of 74 patients, 61%). Overall operative mortality was 1.4% (1/74 patients). Postoperative morbidity occurred in 5 of 74 (7%) patients (empyema, wound infection, deep venous thrombosis, adult respiratory distress syndrome, Horner syndrome).

Eighty-eight patients received chemotherapy: 5 (6%) as induction therapy, 45 (51%) as primary treatment, 29 (33%) as adjuvant treatment, and 9 (10%) for recurrence. Chemotherapy was used in 47% (18/38) of thymomas, 67% (10/15) of neurogenic tumors, 83% (24/29) of germ-cell tumors, and 96% (23/24) of lymphomas. Ninety-seven patients were treated with radiation therapy: 3 (3%) as preoperative therapy, 44 (45%) as primary treatment, 29 (30%) as adjuvant treatment, 6 (6%) for local recurrence, 13 (13%) as palliation of metastases, and 2 (2%) for prophylactic whole-brain radiation. Radiotherapy was used in 71% (27/38) of thymomas, 59% (17/29) of germ-cell tumors, 88% (21/24) of lymphomas, and 47% (7/15) of neurogenic tumors (Fig. 2).

Recurrence was documented in 47 of 91 patients who either had complete resection or complete response to initial treatment. Recurrence occurred in 12 of 25 (48%) patients with thymomas, all of whom initially had invasive tumors. Tumor recurrence was noted in 13 of 24 (54%) patients with germ-cell tumors who initially had a complete response to treatment. Similarly, 13 of 22 (59%) lymphoma patients with initial complete re-

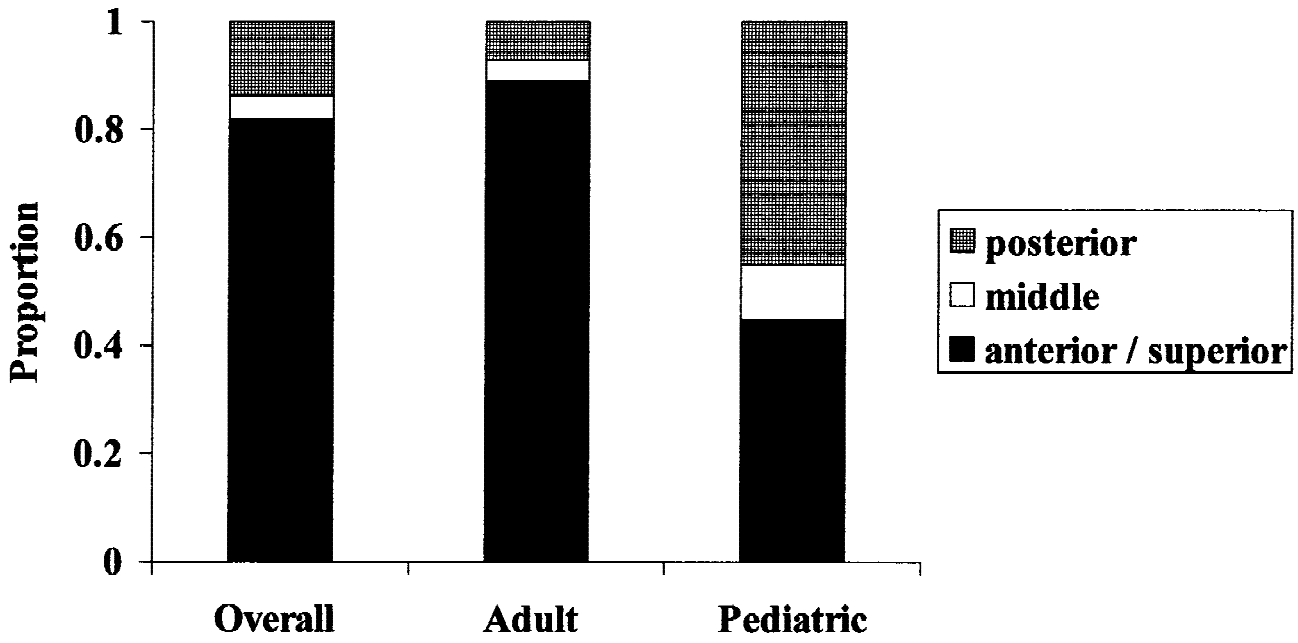

Fig. 1. Mediastinal tumors: location.

TABLE II. Pathology of Mediastinal Tumors

Histology	Overall (n = 124)	Pediatric only (n = 20)
Thymoma	38	2
Germ cell	29	1
Lymphoma	24	6
Neurogenic	15	10
Carcinoma	1	
Sarcoma	6	
Carcinoid	3	
Plasma cell	2	
Cyst	5	
Hyperplasia	1	1

sponses developed recurrence. The median time to recurrence for all tumors was 10 months. In the 47 patients with recurrences, multiple synchronous sites of recurrence developed in 12 of 47 (26%) patients, while the mediastinum or lung were each the sole site of first recurrence in 9 of 47 (19%) patients.

Median follow-up was 25 months and mean follow-up was 60 months. Overall 5-year and 10-year survival rates were 28% and 20%, respectively. Five-year survival was 30% for thymoma, 23% for germ-cell tumors, 29% for lymphomas, and 36% for malignant neurogenic tumors. Median survival for all tumors was 44 months. At the time of analysis, 62% (74/120) of patients had died (64/74, 86% disease-related), and four patients were lost to follow-up. On univariate analysis, negative prognostic factors included presence of symptoms ($P = 0.01$), incomplete resectability ($P = 0.04$), recurrence ($P = 0.00001$), and the presence of distant metastases at presentation ($P = 0.02$). On multivariate analysis, the only factors that independently predicted poor survival were the presence of metastatic disease at presentation ($P = 0.02$) and tumor recurrence ($P = 0.00001$). For germ-cell tumors, patients with seminomas had significantly better survival than those with nonseminomatous tumors ($P = 0.003$).

DISCUSSION

This retrospective review shows similar demographic, clinical presentation, and tumor histology data to that previously published from other institutions [1,2,5–10]. However, our proportion of malignant tumors and stage at time of referral were generally higher than reported in other series. This undoubtedly is a reflection of our tertiary cancer hospital referral pattern. Our series had relatively few lymphomas; our strict policy of only including primary mediastinal lymphomas is probably responsible for this.

We have changed our approach to mediastinal tumors over the last 2 decades [3,11]. Computed tomography is the standard imaging study for mediastinal masses and magnetic resonance imaging is used selectively for possible vascular or spinal cord involvement. Open surgical or mediastinoscopic biopsies were formerly the diagnostic procedures of choice. More recently, selected tumors have been diagnosed by needle biopsies, immunohistochemical studies, and serum tumor markers (alpha-fetoprotein, beta-human chorionic gonadotropin). Benign mediastinal cysts are often suspected on the basis of computed tomography characteristics, and their diagnosis and treatment are often accomplished by minimally invasive surgical techniques [12,13]. All patients with possible

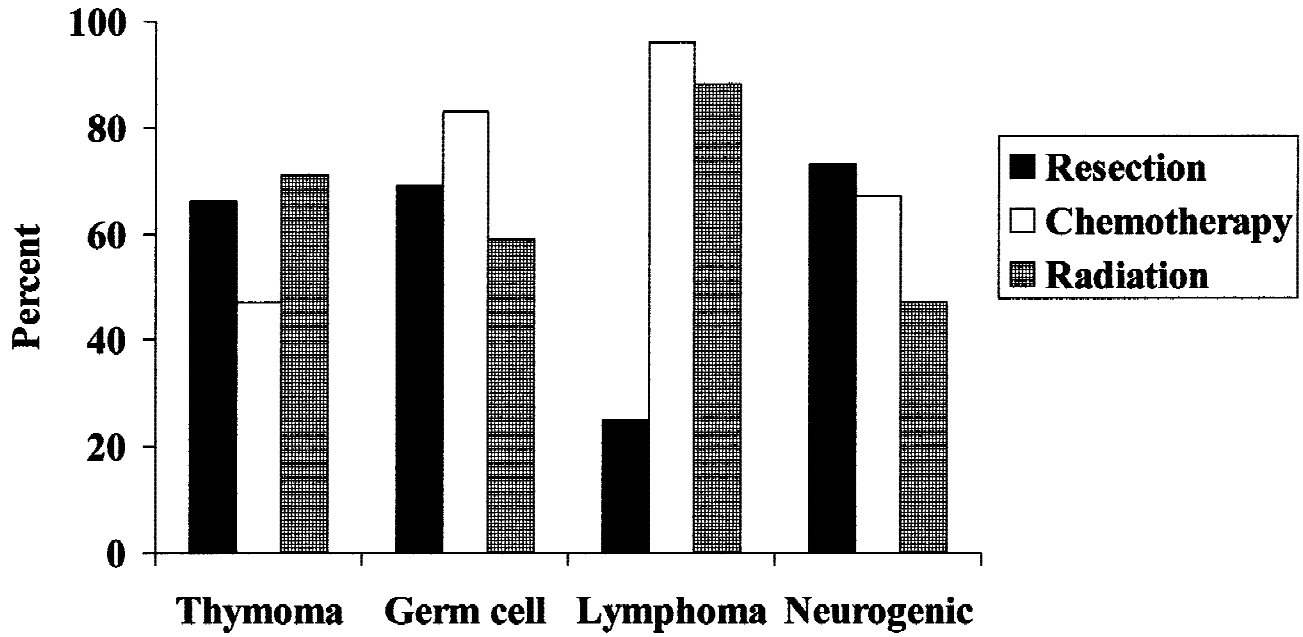

Fig. 2. Mediastinal tumors: multimodality treatment.

thymomas should have clinical assessment for motor weakness and serum antiacetylcholine receptor antibody studies to detect occult myasthenia gravis [14].

In adults, masses in the anterosuperior mediastinum present the greatest diagnostic and treatment challenge for surgical oncologists. The common tumors in this location include thymomas (and other thymic malignancies), germ-cell tumors, and primary mediastinal lymphomas. Multimodality treatment planning should be considered for all of these tumors. Therefore, it is no longer acceptable simply to proceed with a sternotomy for resection, without first carefully considering diagnostic and staging issues and their implications for optimal tumor treatment. This management error remains distressingly common. We restrict initial surgical resection of an anterior mediastinal mass to situations where the tumor is obviously resectable by computed tomography criteria. These tumors usually turn out to be stage I or II thymomas, and surgical resection is an acceptable initial therapy. However, all other anterior mediastinal masses should be evaluated by tumor marker studies and diagnostic needle biopsies [3,11]. Therapy is then planned in a multidisciplinary setting.

Germ-cell tumors are primarily treated with chemotherapy, with surgical resection reserved for residual tumor masses. Primary mediastinal lymphomas are treated with radiotherapy, chemotherapy, or both; resection is not a major component of treatment. At our institution, higher-stage thymomas (invasive into mediastinal structures) and thymic carcinomas are currently treated with induction chemotherapy, surgical resection, and postoperative radiotherapy [15].

Posterior mediastinal tumors are typically neurogenic in nature [1–3]). In adults, they are usually benign tumors. In children, malignant neurogenic tumors are more common. Therefore, our approach to presumed neurogenic tumors in the posterior mediastinum is influenced by age and computed tomography assessment of complete resectability. For seemingly benign, resectable, neurogenic tumors in adults, we proceed directly to resection. However, tumors with radiographic evidence of malignancy or invasion are initially biopsied (CT-guided needle biopsy), and then considered for multimodality treatment.

True middle mediastinal tumors are uncommon. Benign cysts are typically found in this compartment. Lymphomas commonly involve the middle mediastinum, but usually as just one component of a more generalized malignant process. Similarly, metastatic cancers often produce a mass in the middle mediastinum, but these malignancies are not within the customary definition of primary mediastinal tumors. Diagnostic and treatment approaches for middle mediastinal masses are individualized, depending on the pathology suspected [3,12,13].

Malignant mediastinal masses often require multimodality treatment. Therefore, thoughtful diagnostic, staging, and treatment planning is necessary. Despite improvements in survival with multimodality treatment for most mediastinal malignancies, many patients ultimately die of recurrent tumor.

REFERENCES

1. Davis RD, Oldham HN, Sabiston DC: Primary cysts and neoplasms of the mediastinum: Recent changes in clinical presenta-

tion, methods of diagnosis, management, and results. Ann Thorac Surg 1987;44:229–237.
2. Cohen AJ, Thompson L, Edwards FH, et al.: Primary cysts and tumors of the mediastinum. Ann Thorac Surg 1991;51:378–386.
3. Luketich JD, Ginsberg RJ: The current management of patients with mediastinal tumors. Adv Surg 1997;30:311–332.
4. Kaplin EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
5. Wychulis AR, Payne WS, Clagett OT, et al.: Surgical treatment of mediastinal tumors: A 40-year experience. J Thorac Cardiovasc Surg 1971;62:379–392.
6. Ovrum E, Birkeland S: Mediastinal tumors and cysts: A review of 91 cases. Scand J Thorac Cardiovasc Surg 1979;13:161–168.
7. Nandi P, Wong KC, Mok CK, et al.: Primary mediastinal tumors: Review of 74 cases. J R Coll Surg Edinb 1980:25:460–466.
8. Azarow KS, Pearl RH, Zurcher R, et al.: Primary mediastinal masses: A comparison of adult and pediatric populations. J Thorac Cardiovasc Surg 1993;106:67–72.
9. Adkins RB, Maples MD, Haisworth JD: Primary malignant mediastinal tumors. Ann Thorac Surg 1984;38:648–659.
10. Mullen B, Richardson JD: Primary anterior mediastinal tumors in children and adults. Ann Thorac Surg 1986;42:338–345.
11. Strollo DC, Rosado de Christenson ML, Jett JR: Primary mediastinal tumors. Part 1. Tumors of the anterior mediastinum. Chest 1997;112:511–522.
12. Roviaro G, Rebuffat C, Varoli F, et al.: Videothoracoscopic excision of mediastinal masses: Indications and technique. Ann Thorac Surg 1994;58:1679–1684.
13. Urschel JD, Horan TA: Mediastinoscopic treatment of mediastinal cysts. Ann Thorac Surg 1994;58:1698–1701.
14. Urschel JD, Grewal RP: Thymectomy for myasthenia gravis. Postgrad Med J 1998;74:139–144.
15. Venuta F, Rendina EA, Pescarmona EO, et al.: Multimodality treatment of thymoma: A prospective study. Ann Thorac Surg 1997;64:1585–1592.